12. (Amended) A composition, characterized in that it includes a protein according to any one of Claims 1 [and] or 3-5[, and optionally] in combination with an [additives] additive or [carriers] carrier.

13. (Amended) A pharmaceutical composition, characterized in that it includes a protein according to any one of Claims 1 [and] or 3-5[, and optionally] in combination with a pharmaceutically acceptable carrier or extender.

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1, 3-5 and 11-13 are pending. Claims 1, 4, 5 and 11-13 have been amended to more clearly define the subject matter of the present invention without prejudice to the filing of any divisional, continuation, or continuation-in-part application. In particular, the term "variants" has been deleted from claims 1 and 5 and the reference to domains chosen from among functionally similar proteins, variants, subfragments, multiples or mixtures has been eliminated from claim 4. Claims 11-13 have been amended to correct typographical errors and to recite the presence of a second component of the claimed kits and compositions. Support for these amendments may be found, for example, on page 13, line 1 - page 14, line 3 of the specification as filed. No new matter has been added.

OBJECTIONS TO THE DISCLOSURE

The Examiner has objected to a series of informalities in the disclosure. In particular, the Examiner has identified misspellings and a reference to the claims within the specification. In addition, the Examiner objected to the arrangement of the specification. Applicants have amended the specification to correct these errors and to arrange the specification appropriately. Accordingly, applicants submit that this objection has been overcome.

REJECTIONS UNDER 35 U.S.C. § 101

The Examiner rejected claim 1 under 35 U.S.C. § 101, as being directed to non-statutory subject matter. In particular, the Examiner believes that the protein in claim 1 has the same characteristics and utility as a protein found naturally, and therefore does not constitute as patentable subject matter.

Applicants respectfully traverse this ground for rejection. Briefly, a protein L as recited in claim 1 comprises certain portions (*i.e.,* B1-B5) of a naturally occurring protein L. The claimed protein L does not, however, contain the complete, naturally-occurring, endogenous protein. In particular, an endogenous protein L contains, in addition to B1-B5, an N-terminal region A, and C-terminal regions C1, C2, W and M (*see* the schematic representations provided in Figures 4 and 5 of the present application). Only a small portion (*i.e.,* four amino acid residues) of the N-terminal A region is present in the claimed protein, and none of the amino-terminal regions are included. To clarify this distinction, the term "variants" has been eliminated from claim 1. Accordingly, claim 1 as amended does not encompass a naturally occurring protein, and applicants respectfully submit that this ground for rejection has been obviated.

OBVIOUSNESS-TYPE DOUBLE PATENT REJECTIONS

The Examiner rejected claims 1 and 11-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 4,876,194. The Examiner believes that, although the cited claims are not identical to those presently pending, they are not patentably distinct. The Examiner also rejected claims 3-5 as being unpatentable over claims 1-14 of U.S. Patent No. 4,876,194 in view of Guss et al. and Kastern et al. The Examiner believes that it would be obvious to one of ordinary skill in the art at the time the invention was made to link protein L, as taught by U.S. Patent No. 4,876,194, with protein G or the C1, C2 or C3 domains taught by Guss et al.

Applicants respectfully traverse these grounds of rejection. Briefly, in order to render claims obvious, the cited references teach or suggest the claimed invention (*see In re Vaeck*, 947 F2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991)). In this instant case, the cited

references do not meet this requirement. In particular, while U.S. Patent No. 4,876,194 does teach and enable the construction of proteins which have an apparent molecular of 95,000 kDA, as well subfragments thereof, it does not teach or suggest the presently claimed sequence recited in claim 1. Addition of references by Guss et al. and Kastern et al. do not remedy the deficiency of the primary reference. Accordingly, applicants respectfully submit that the rejection of claims 1 and 11-13 under the judicially created doctrine of obviousness-type double patenting has been traversed.

REJECTIONS UNDER 35 U.S.C. § 112

The Examiner rejected claims 3 and 11-13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and claim the subject matter which is regarded as the invention. In particular, the Examiner believes that it is not clear what constitutes a domain which binds to heavy chains in immunoglobulin G. The Examiner also believes that claims 11-13 are indefinite because a kit or composition should comprise two or more products.

Applicants respectfully traverse this ground for rejection. Briefly, the specification provides that domains that bind to heavy chains in immunoglobulin G are chosen from the C1-, C2- and C3-domains in protein G; the A-, B- and C1-domains from protein H; the A-, B1-, B2- and S-domains in protein M1 and the E-, D-, A-, B- and C-domains in protein A, as well as variants, subfragments, multiples or mixtures of these domains that have the same binding properties (*see* page 6, lines 1-8 of the specification). These domains, and suitable variants, subfragments, multiples and mixtures, may be readily identified, based upon the disclosure of the subject application, and the binding assays provided therein. Accordingly, applicants respectfully submit that one of ordinary skill in the art would readily understand the scope of the recited domains, and that this ground for rejection has been obviated.

Further, claims 11-13 have been amended to recite the presence of a second component. Within claim 11, the reagent kit now comprises a protein L and a detection reagent for use in detecting protein L bound to an immunoglobulin. Claims 12 and 13 have

been amended to encompass only compositions that comprise an additional additive or carrier. Applicants therefore submit that the rejection of claims 11-13 has been obviated.

The Examiner rejected claims 1, 3-5 and 11-13 under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner is of the view that the specification does not adequately teach which modifications can be made in the protein L sequence while retaining the activity and utility of the protein. The Examiner appears to be concerned that the application does not disclose the general tolerance to modification, specific positions that can be predictably modified or specific modifications that are likely to be successful. Thus, the Examiner believes that it would require undue experimentation to identify modified proteins having the recited binding properties.

Applicants respectfully traverse this ground for rejection. Although applicants believe that the claims prior to the present Amendment are fully enabled by the specification, in order to facilitate prosecution applicants have deleted the term "variants" from claims 1 and 5. This amendment also extends to claims 3, 4 and 11-13, which depend from claim 1. Claims 1 and 5, as amended, encompass protein L having a recited sequence or "subfragments, multiples or mixtures of the domains B1-B5 having the same binding properties." Subfragments are defined within the specification as portions of the recited domains (page 6, lines 10-12); multiples are proteins having several arrays of the binding domains (page 6, lines 17-19) and the term "mixture" refers to a combination of separate domains, in accordance with its common meaning. Techniques for preparing such subfragments, multiples and mixtures are well known in the art.

The Examiner's primary concern appears to focus on the ability to predict the properties of a given subfragment, multiple or mixture. In this regard, applicants wish to point out that such a prediction is unnecessary. The binding properties of a particular subfragment, multiple or mixture may be readily assessed utilizing techniques such as those provided in the representative assays of Example 3. Applicants respectfully submit that, given the disclosure of the subject application, one of ordinary skill in the art could, without undue experimentation, readily determine which subfragments, multiples and mixtures retain the binding properties of a protein comprising domains B1-B5 of protein L. Accordingly,

applicants submit that the rejection of claims 1, 3-5 and 11-13 under 35 U.S.C. § 112, first paragraph has been traversed.

REJECTIONS UNDER 35 U.S.C. § 102(a)

The Examiner rejected claims 1 and 11-13 under 35 U.S.C. § 102(a) as being anticipated by Kastern et al. (*J. Biol. Chem. 267*:12820-25, 1992). In particular, the Examiner is of the view that Kastern et al. disclose protein L and fragments thereof capable of binding light chains of immunoglobulins, as well as reagent kits and pharmaceutical compositions comprising such proteins.

Applicants respectfully traverse this ground for rejection. Applicants wish to point out that Kastern et al. 1992 is the work of the present inventors, and is not prior art under 35 U.S.C. § 102(a). In particular, applicants are preparing and will shortly submit a declaration which states that the work of Kastern et al. is that of the named inventors, and therefore, is not prior art under 35 U.S.C. § 102(a). Accordingly, Kastern et al. 1992 is not prior art, and applicants respectfully submit that this ground for rejection has been traversed.

REJECTIONS UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 1 and 11-13 under 35 U.S.C. § 102(b) as being anticipated by EP 0 255 497. In particular, the Examiner believes that EP 0 255 497 discloses a protein L and subfragments with immunoglobulin-binding activity, as well as a reagent kit and pharmaceutical composition comprising such proteins.

Applicants respectfully traverse this ground for rejection. Briefly, EP 0 255 497 is directed to an isolated protein L. As noted above, a protein L within the pending claims contains domains B1-B5, but does not contain the amino and carboxy terminal portions of naturally occurring protein L. Accordingly, the recited claims do not encompass the protein L of EP 0 255 497. In addition, while EP 0 255 497 mentions subfragments with immunoglobulin-binding activity, the published application does not teach or suggest the sequence of protein L. Accordingly, applicants respectfully submit that this ground for rejection has been traversed.

The Examiner rejected claims 1 and 11-13 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,876,194 ('194). In particular, the Examiner is of the view that '194 discloses a protein L and subfragments with immunoglobulin-binding activity. The Examiner notes that '194 does not disclose an amino acid sequence as recited in the pending claims, but believes that the scope of "variants" encompasses the protein L of '194.

Applicants respectfully traverse this ground for rejection. Briefly, in order to anticipate a claim under 35 U.S.C. § 102(b), a cited reference must disclose each and every element of the claimed invention. In the instant case, the disclosure of '194 is directed to a wild-type protein L, but does not provide the sequence of that protein. Accordingly, the protein L of '194 is not encompassed by the pending claims, and applicants respectfully submit that this ground for rejection has been overcome.

REJECTIONS UNDER 35 U.S.C. § 103

The Examiner also rejected claims 4-6 under 35 U.S.C. § 103(a) as being unpatentable over several combinations of references. Before addressing each rejection specifically, applicants wish to emphasize several unique aspects of the present invention. Briefly, the present invention is based on the identification and characterization of the portions of protein L that bind to light Ig chains. This work was unusually difficult. The sequencing of protein L and the subsequent identification of the Ig-binding domains represents a major scientific breakthrough, as evidenced by the publication of this work in the Journal of Biological Chemistry, which is one of the most cited scientific journals in the world.

Further, the hybrid proteins containing one or more of the B1-B5 domains and one or more domains that bind to heavy chains in immunoglobulin G unexpectedly have immunoglobulin-binding features that are superior to those of the parts (*i.e.*, protein L and protein G). In addition, it should be noted that that hybrid molecules comprising Ig-binding domains of protein L have binding properties that are superior to previously described Ig-binding proteins. In particular, protein L binds to about 50% of all light Ig chains. Since these light chains are shared by all classes of immunoglobulins (IgG, IgM, IgA, IgD and IgE),

protein L binds to about 50% of all antibodies, irrespective of Ig class. In contrast, protein A and protein G mainly bind to IgG. A hybrid protein comprising light Ig-binding domains of protein L and IgG-binding domains (*e.g.,* from protein A, G, H, M1 etc.) binds to both IgG and to antibodies of the type IgM, IgA, IgD and IgE. Such a protein is able to bind to 89% of all human antibodies, since IgG is the quantitatively dominating Ig class. A hybrid LG protein is also capable of binding to antibody fragments (*e.g.,* Fab and Fv). Thus, the hybrid proteins of the present invention possess binding properties that are unique and unexpectedly superior to the properties of their component parts.

With regard to the specific rejections, the Examiner has rejected claims 4-6 under 35 U.S.C. § 103(a) as being unpatentable over EP 0 255 497 and further in view of Kastern et al. 1990 (*Infection and Immunity 58*(5):1217-22) and Guss et al. (WO 87/05361). In particular, the Examiner believes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to link protein L as taught by EP 0 255 497 with protein G or the C1, C2, C3 domains as set forth by Guss et al. since, as taught by Kastern et al. 1990, protein L reacts with all classes of immunoglobulin.

Applicants respectfully traverse this ground for rejection. As noted above, EP 0 255 497 fails to disclose the sequence of the Ig-binding domains of protein L, the identification of which was unexpectedly difficult. EP 0 255 497 also fails to teach or suggest combining such regions with domains of other proteins. Kastern et al. and Guss et al. do not remedy these deficiencies. Kastern et al. describes studies in which the expression of protein L is assayed in a clinical collection of *P. magnus* strains. Only a partial sequence of protein L is provided (96 amino acids out of a total of 716 amino acids), and that sequence does not appear in the B1-B5 region. There is no suggestion within Kastern et al. that the disclosed partial sequence is involved with the immunoglobulin-binding of protein L. On the contrary, the disclosed sequence shows similarity with parts of protein G lacking Ig-binding activity (*see* page 1221, left hand column, lines 1-7). Guss et al. is directed to the C1, C2 and C3 domains of protein G, and to fusion proteins of protein A and protein G, and does not disclose or suggest combinations with domains of protein L. Thus, none of the cited references teach or suggest the identity of protein L Ig-binding domains or the superior

binding properties of the hybrid protein containing domains of protein L and protein G. Accordingly, applicants respectfully submit that this ground for rejection has been traversed.

The Examiner rejected claims 4-6 under 35 U.S.C. § 103(a) as being unpatentable over Kastern et al. 1992 (*J. Biol. Chemistry 267*(18):12820-25, 1992) and Guss et al. In particular, the Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to link protein L as taught by Kastern et al. 1992 with protein G or the C1, C2, or C3 domains as set forth by Guss et al. since, as taught by Kastern et al. 1992, protein L has a broader Ig binding activity than protein G.

Applicants respectfully traverse this ground for rejection. Applicants wish to point out, as noted above, that Kastern et al. 1992 is the work of the present inventors, and is not prior art under 35 U.S.C. § 103. Further, as noted above, Guss et al. does not teach or suggest the combination of protein G or domains thereof with protein L domains, or the unexpected properties of such a hybrid protein. Accordingly, applicants submit that this ground for rejection has been traversed.

Finally, the Examiner rejected claims 4-6 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,876,194 and Guss et al. (WO 87/05361). More specifically, similar to the above rejections, the Examiner asserted that it would be obvious to link the protein L of U.S. Patent No. 4,876,194 with the protein G of Guss et al.

Applicants respectfully traverse this ground for rejection. As discussed above, the disclosure of '194 is directed to a wild-type protein L, and does not teach or suggest the sequence of that protein or the identity of the Ig-binding domains. The '194 patent also fails to teach or suggest combining such regions with domains of other proteins or the superior binding properties found to be possessed by a hybrid protein. Guss et al. does not remedy these deficiencies, being directed solely to the C1, C2 and C3 domains of protein G and to a protein A-protein G fusion protein. Accordingly, applicants respectfully submit that this ground for rejection has been overcome.

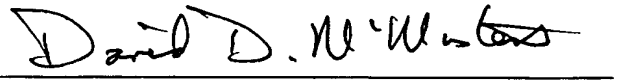
On the basis of the above amendment and remarks, reconsideration of the application and its allowance are respectfully requested. Should the Examiner have any

additional questions, he is respectfully encouraged to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

Lars Björck and Ulf Sjöbring

SEED and BERRY LLP



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